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Published in:

Seminars in Arthritis and Rheumatism

DOI:

[10.1016/j.semarthrit.2017.09.006](https://doi.org/10.1016/j.semarthrit.2017.09.006)

Publication date:

2018

Document version

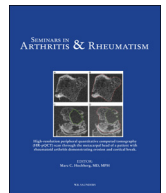
Publisher's PDF, also known as Version of record

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Citation for published version (APA):

Hawley, S., Cordtz, R., Dreyer, L., Edwards, C. J., Arden, N. K., Delmestri, A., ... Prieto-Alhambra, D. (2018). Association between NICE guidance on biologic therapies with rates of hip and knee replacement among rheumatoid arthritis patients in England and Wales: An interrupted time-series analysis. *Seminars in Arthritis and Rheumatism*, 47(5), 605-610. <https://doi.org/10.1016/j.semarthrit.2017.09.006>



Association between NICE guidance on biologic therapies with rates of hip and knee replacement among rheumatoid arthritis patients in England and Wales: An interrupted time-series analysis

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ARTICLE INFO

Keywords:

Pharmacoepidemiology
Rheumatoid arthritis
Biologic therapy
Arthroplasty of hip
Arthroplasty of knee

ABSTRACT

Objective: To estimate the impact of NICE approval of tumor necrosis factor inhibitor (TNFi) therapies on the incidence of total hip replacement (THR) and total knee replacement (TKR) among rheumatoid arthritis (RA) patients in England and Wales.

Methods: Primary care data [Clinical Practice Research Datalink (CPRD)] for the study period (1995–2014) were used to identify incident adult RA patients. The age and sex-standardised 5-year incidence of THR and TKR was calculated separately for RA patients diagnosed in each six-months between 1995–2009. We took a natural experimental approach, using segmented linear regression to estimate changes in level and trend following the publication of NICE TA 36 in March 2002, incorporating a 1-year lag. Regression coefficients were used to calculate average change in rates, adjusted for prior level and trend.

Results: We identified 17,505 incident RA patients of whom 465 and 650 underwent THR and TKR surgery, respectively. The modeled average incidence of THR and TKR over the biologic-era was 6.57/1000 person years (PYs) and 8.51/1000 PYs, respectively, with projected (had pre-NICE TA 36 level and trend continued uninterrupted) figures of 5.63/1000 PYs and 12.92 PYs, respectively. NICE guidance was associated with a significant average decrease in TKR incidence of $-4.41/1000$ PYs (95% C.I. -6.88 to -1.94), equating to a relative 34% reduction. Overall, no effect was seen on THR rates.

Conclusions: Among incident RA patients in England and Wales, NICE guidance on TNFi therapies for RA management was temporally associated with reduced rates of TKR but not THR.

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Key messages

- In England and Wales, TNFi approval for RA was associated with reduced TKR rates.
- In England and Wales, no change in THR rates was seen following TNFi approval.

- Further studies in non-UK settings are required to validate these findings.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease associated with pain, stiffness and swelling in affected joints [1]. Joint damage is a central feature of RA [2], estimated to account for

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approximately 25% of disability in established disease [3]. Data from the mid-late 20th century indicate that over half of incident RA patients required RA-related surgery over 30 years of follow-up [4]. Despite some evidence suggesting that joint erosions can heal over time [3], such healing is generally rare [5] and reducing the risk of irreversible joint damage through early and 'treat-to-target' disease management is emphasized in numerous guidelines.

The literature widely recognizes that the availability of biological disease modifying anti-rheumatic drugs (bDMARDs) over recent decades has revolutionised the management of RA [6–8]. A wealth of randomized controlled trial (RCT) data has conclusively demonstrated the beneficial impact of bDMARDs on ACR response criteria and structural joint damage [8,9]. However, no such data exists concerning the impact of bDMARDs on the need for joint replacement—a costly consequence of joint failure that is not without its risks. During the "biologic era" there has been an emerging body of observational studies indicating that the number and/or incidence of RA-related joint surgery has generally been decreasing across numerous developed countries [10–20]. Although the use of biologic therapies has been routinely offered as an explanatory factor, their role is not clear and estimation of their impact on the incidence of joint replacement remains lacking.

It has previously been suggested that when an RCT is likely to be unfeasible, a strong research alternative is to take advantage of naturally occurring events such as a national health policy change in order to carry out a quasi-experiment [21]. In this context, our aim was to estimate the impact of the national institute for health and care excellence (NICE) approval of tumor necrosis factor inhibitor (TNFi) therapy [22] on the temporal trends of total hip (THR) and total knee replacement (TKR) among RA patients in England and Wales.

Methods

Study population and data sources

We used primary care health data from the Clinical Practice Research Datalink (CPRD) for the period Apr 1995 to Sept 2014. As of 2013, CPRD covered over 11.3 million patients from 674 UK practices and had a representative coverage of approximately 7% of the United Kingdom [23]. Where available, we obtained linked secondary care Hospital Episode Statistics (HES) data for the same time period. Approximately 58% of UK CPRD practices participate in the CPRD linkage scheme [23] and previous research by CPRD has shown that linked practices/patients are representative of the CPRD population as a whole. HES data contains hospital admission records relating to each 'finished consultant episode'—the period of time an individual spends under the care of one NHS consultant. Mortality data were linked to the Office for National Statistics (ONS) database.

Incident RA patients within the study period were identified using a pre-defined READ code list (Appendix Table 1), as developed elsewhere [24], with the date of first recorded RA considered as diagnosis date. Data on BMI, smoking status and Charlson comorbidity score at date of RA diagnosis was also extracted from CPRD. Patients with either a prior or subsequent diagnosis of a different inflammatory arthritis (lupus, ankylosing spondylitis, psoriatic arthritis or crystal arthropathy) were excluded due to possible diagnosis or coding errors. Patients aged < 18 years old were also excluded as were patients registered in a general practitioner (GP) practice outside England or Wales given that compliance to NICE guidance is only mandatory for these countries (Appendix Fig. 1).

Intervention

Our defined intervention was the publication of the NICE technology appraisal (TA) 36 in March 2002. This provided

guidance on the use of TNFi (etanercept and infliximab) for the treatment of RA, and stated that these therapies were recommended options for the treatment of adults with severe RA (Disease Activity Score (DAS) > 5.1) who had already failed to respond to two conventional synthetic disease modifying anti-rheumatic drug (csDMARD) therapies.

Outcomes

We used CPRD Read codes as used previously [25,26] to identify the occurrence of first THR and TKR after incident RA diagnosis. THR and TKR were considered separately so patients could potentially have both outcomes of interest. For validation purposes, we also identified first subsequent THR and TKR within the HES data using the classification of interventions and procedures coding system (OPCS4). Reporting of THR and TKR in HES has previously been shown to be comparable with the National Joint Registry (NJR) [27].

Statistical analysis

To assess the validity of the THR and TKR Read codes, we calculated sensitivity and specificity among the 62.6% of RA patients with both CPRD and HES data (Appendix Fig. 1), considering HES as the reference standard. Agreement was defined as surgeries present in both data sources within a 60-day time period, with 30-day and 90-day time periods also explored. Given that good agreement was found (Appendix Table 2), we proceeded to use THR and TKR as reported in CPRD for the main analysis, and the whole study population (including those with no linked HES) were included.

An age and sex standardised time-series was derived by calculating 5-year incidence rates of THR and TKR among newly diagnosed RA patients within each 6 months between 1995 and 2009. We only concentrated on the first 5 years after diagnosis so that patients contributed the same follow-up irrespective of when they were diagnosed to allow valid rate comparisons throughout the study period. Patients were followed up from date of diagnosis until the first date of: outcome event, death, loss to follow-up or 5 years of follow-up.

A segmented linear regression was performed on the aggregated standardised time-series to estimate two parameters of interest associated with the publication of NICE TA 36: change in subsequent level of outcome and change in subsequent trend [28]. Given that the NICE guidance recommended that only patients having a failed response to two (6 month) trials of csDMARD therapy should initiate a TNFi, a 1-year lag period following March 2002 was decided upon a-priori in which data were removed from the time-series. The regression model was specified as following: $Y_t = \beta_0 + \beta_1 * \text{time}_t + \beta_2 * \text{intervention}_t + \beta_3 * \text{post_intervention_time}_t + e_t$. Here, Y_t is the 5-year incidence among RA patients diagnosed at time point (i.e., 6-monthly period) t . β_0 estimates the baseline level of the outcome just before the beginning of the time series. β_1 estimates the pre-intervention trend, β_2 the change in level between the time point immediately before vs. after the lag period and β_3 the change in trend occurring immediately after the lag period. Analyses were based on 14 pre-intervention data points (Apr 1995–Mar 2002) and 13 post-intervention data points (Apr 2003–Sept 2009). Final model specification was derived using a backward-stepwise approach (p -entry 0.049; p -exit 0.20) to remove non-significant regression terms in order to maximize statistical power, although results from full models were also reported. Durbin-Watson statistics indicated no significant autocorrelation.

Regression coefficients were used to estimate an overall intervention effect by predicting what would have been observed post-intervention (i.e., counterfactual rates) had pre-intervention levels

and/or trends continued uninterrupted, and comparing this with what was modeled using observed post-intervention data [28,29]. The midpoint of the post-intervention period was used to calculate the average difference over the post-intervention time points.

Sensitivity analyses

Due to likely delay in implementation of NICE recommendations, a 2-year lag period was used in a sensitivity analysis. A data-driven (with no pre-specified time point/intervention) approach was also conducted using a Joinpoint analysis in order to identify where—if at all—any changes in trend occurred [30]. An uncorrelated errors model was specified, using the grid search method with a maximum of one Joinpoint and minimum of eight observations before and after (as recommended for an interrupted time series approach). Model selection was carried out using permutation tests (Monte Carlo methods) with a significance level set to 0.05.

Results

Between 1995 and 2014 there were 23,830 incident RA patients identified, of whom 10,952 had HES linkage (Appendix Fig. 1). Considering HES as the reference standard, THR in CPRD had 80.1% sensitivity and 98.4% specificity whilst TKR in CPRD had 83.5% sensitivity and 98.1% specificity (Appendix Table 2).

Included in the interrupted time series analysis were 17,505 incident RA patients diagnosed in CPRD between 1995 and 2009 (Appendix Fig. 1). Patient characteristics are presented in Appendix Table 3. Mean age at RA diagnosis increased slightly from 58.7 in 1995 to 60.3 in 1999 ($p = 0.065$), whilst the gender ratio remained fairly stable over the same time frame (70.4% to 66.3% female; $p = 0.12$). Prevalence of obesity (BMI ≥ 30), as reported at time of RA diagnosis, increased from 11.5% in 1995 to 22.1% in 2009 ($p \leq 0.001$), whilst concurrent smoking status decreased from 27.9% to 20.9% ($p = 0.011$). Overall there were 465 THRs and 650 TKRs occurring within 5 years of RA diagnosis (Fig. 1), yielding a crude incidence rate of 6.16/1000 person years (PYs) (95% CI: 5.63–6.75) and 8.65/1000 PYs (95% CI: 8.01–9.34), respectively. Median follow-up over the 5 years following RA diagnosis was 5.00 years (inter quartile range (IQR): 3.69–5.00) for THR and 5.00 years (IQR: 3.60–5.00) for TKR, with median time-to-event being 1.96 (IQR: 0.95–3.24) and 2.32 (IQR: 1.02–3.58), respectively. Average mortality over the same time frame was 15.5% while loss-to-follow-up was 18.2%.

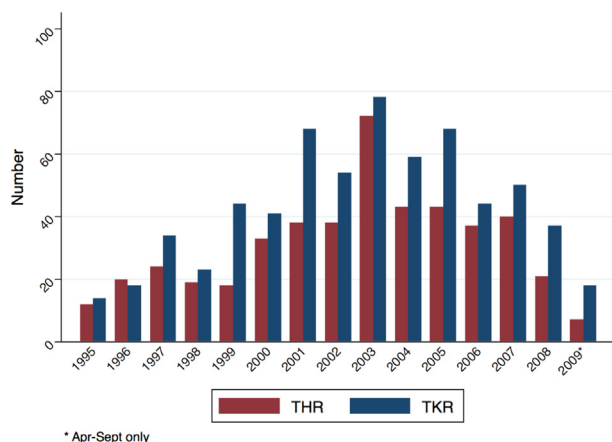


Fig. 1. Number of RA patients undergoing THR/TKR surgery within 5 years: stratified by year.

Table 1

Temporal trends in joint replacement rates among 17,505 incident rheumatoid arthritis patients diagnosed from 1995 to 2009 (per 1000 person-years)

Parameter	Coefficient	Lower 95% CI	Upper 95% CI	p value
<i>Total hip replacement</i>				
Intercept	5.63	4.73	6.52	< 0.001
Trend ^a	–	–	–	–
Level change after NICE TA 36	3.97	1.79	6.14	0.001
Trend change after NICE TA 36 ^a	–0.47	–0.71	–0.22	0.001
<i>Total knee replacement</i>				
Intercept	5.89	3.83	7.94	< 0.001
Trend ^a	0.31	0.11	0.51	0.004
Level change after NICE TA 36	–	–	–	–
Trend change after NICE TA 36 ^a	–0.68	–1.08	–0.28	0.002

– = $p \geq 0.2$.

^a per 6 months.

Age and sex standardised 5-year incidence of THR at the start of the study period was 5.63/1000 PYs (95% CI: 4.74–6.54), which remained unchanged during the pre-TNFi period (Apr 1995–Mar 2002) (Table 1 and Fig. 2A). Immediately following the intervention lag period there was a level increase in the incidence rate by 3.97/1000 PYs (95% CI: 1.79–6.14) but a subsequent downward trend of –0.47/1000 PYs (95% CI: –0.71–0.22) per 6 months for the remainder of the post-NICE TA36 time period. Based on these coefficients, the estimated incidence of THR at the mid-point of the post-NICE TA36 time period was 6.57/1000 person years (PYs). The incidence at the same time point estimated solely by extrapolating the pre-NICE TA36 level and trend was 5.63/1000 PYs, therefore translating to no significant average change in rates (0.95/1000 PYs (95% CI: –2.66 to 4.56)).

The incidence of TKR was 5.89/1000 PYs (95% CI: 3.83–7.94) at the start of the study period, which increased by 0.31/1000 PYs (95% CI: 0.11 – 0.51) per 6 months during the pre-intervention period (Table 1 and Fig. 2B). Immediately following the 1-year lag period there was a significant downward change in the prior upward trend by –0.68/1000 PYs (95% CI: –1.08 to –0.28) per 6 months. Based on these coefficients the modeled incidence for the midpoint of the post-intervention period was 8.51/1000 PYs, which was a significant 4.41/1000 PYs (95% CI: 6.88–1.98) lower compared to that estimated, had pre-intervention trends continued uninterrupted (Table 2). This equated to an approximate relative 34% reduction.

In sensitivity analyses using a 2-year lag, THR rates remained flat during the study period while results for TKR remained unchanged from the main analysis (Appendix Fig. 2). Conversely, Joinpoint analysis identified significant inflections in upward trends in the incidence of both THR and TKR, at the time points spanning Oct 2005–Mar 2006 ($P = 0.034$) and Apr 2001–Sep 2001 ($P = 0.036$), respectively. Results from the main analysis using full models were unchanged as when using parsimonious models (Appendix Table 4).

Discussion

Our results indicate that the introduction of TNFi therapies for the management of RA was associated with a significant reduction in TKR but not THR incidence among early RA patients within England and Wales. Specifically, whilst TKR incidence was increasing prior to TNFi approval, this upward trend was reversed following the start of the biologic era, yielding a relative 34% average reduction compared to counterfactual rates. The relationship between THR incidence and TNFi approval was less clear, with

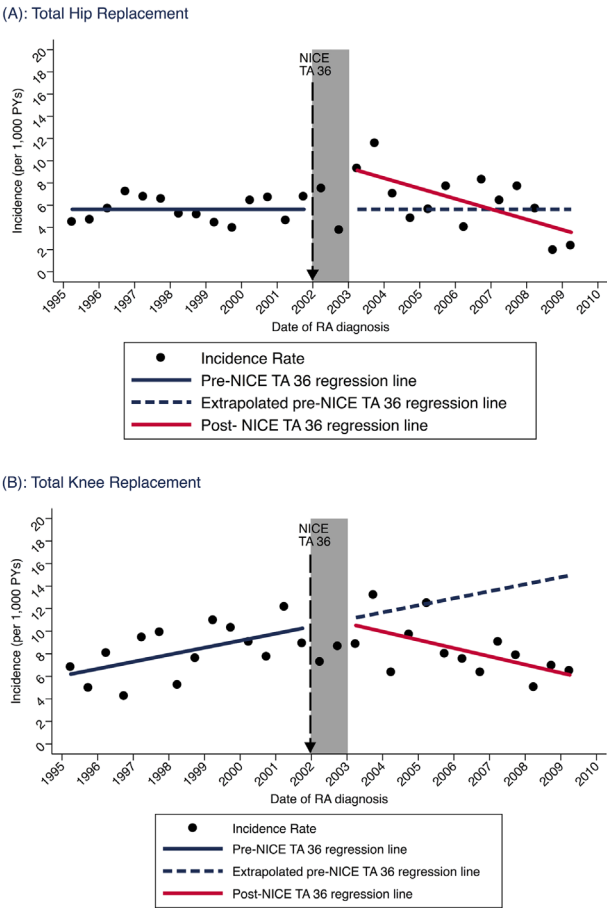


Fig. 2. Standardised incidence of joint replacement within 5 years: (A) THR and (B) TKR.

no significant average change in post-NICE TA 36 modeled rates compared to counterfactual values.

Treatments recommended by a NICE TA publication “as an option” should be available for use in the NHS within 3 months of the guidance being published [31]. Although in reality this may not be the case for a particular patient due to delayed implementation at a local level, a population-level increase in the use of etanercept and infliximab (in line with the recommendations) would be expected [32,33] given the authoritative and widespread reach of NICE.

The potential impact of TNFi therapy on need for joint replacement was not mentioned in the NICE TA 36 document, although the evidence base referred to indicates the plausibility of such a

relationship. For example, results from a high quality RCT were summarized, in which 31% of patients on methotrexate alone experienced progression of structural damage at 54 weeks, whilst this was only 8% for patients on methotrexate plus infliximab [22]. Indeed, the clinical effectiveness of both these therapies in terms of reduced erosive damage is well established [34–36] and joint replacement has been suggested as an important consideration in future economic modeling of the management of RA with bDMARDs [8,37].

Our decrease in TKR rates is consistent with data from the UK NJR which indicate the percentage of knee replacements for which RA was an indication fell from 3% to 2% (2004–2010) [10,38]. Our data also complements and builds on prior studies from elsewhere in Europe and the US. Notably, in the Republic of Ireland the number of THR and TKR surgeries was found to increase dramatically from 1995 to 2010, whilst the number of those with a diagnosis of RA significantly decreased for TKR but remained stable for THR [18]. A similar study from the US found significant reductions in the number of both TKR and THR patients who had RA as the primary diagnosis at surgery, whilst the numbers of TKR and THR for other reasons profoundly increased [16]. Similar arthroplasty trends were reported in most (Norway [39] and Finland [13]) but not all (Sweden [19]) Scandinavian countries.

We found the overall incidence of THR to be lower than TKR, which is supportive of milder RA involvement at the hip [40] and which may explain why TNFi approval was here associated with reduced rates of TKR but not THR. Previous estimates of hip joint synovitis in early RA range between approximately 20% and 40% [41,42], which is considerably lower than the 60% estimated for the knee [43]. Also worth mentioning is that while the knee joint featured in the 1987 ACR classification criteria and Disease Activity Score 28, the hip joint did not [44,45].

However, our lack of access to joint replacement rates for the general population is a key limitation to our study. As such we recognize the need for caution in interpreting our findings. For example, it may be that the approximately stable incidence of THR we observed for RA patients may be a favorable outcome were THR incidence in the general population to have undergone a significant concurrent increase. Indeed, previous NJR data for the general population indicate an overall year-on-year increase in the raw number of both THR and TKR procedures carried out from 2003 to 2012 [46].

Furthermore, in evaluating the impact of NICE guidance on biologics, we cannot rule out other factors such as prescription rates of csDMARDs having markedly increased within this population [47], which may have contributed to a reduced need for joint replacement [48]. Improvement in non-therapeutic aspects of RA management and increased awareness may likewise have played a role [49], as may a gradually declining disease severity or changes in smoking prevalence or BMI, although we consider these reasons insufficient to explain the relatively sudden inflection observed in the TKR trend following NICE recommendations [50]. Another intriguing possibility is that the mere availability of bDMARDs may have given rise to a greater impetus among clinicians to diagnose RA earlier in its natural history, and thereby contributed to a decline in 5-year TKR rates. Whilst unfortunately we do not have data on disease severity, we found the average comorbidity index to worsen over the study period and there was no evidence for a boom in incident RA diagnoses associated with the advent of biologics (Appendix Table 3). It is also reassuring that the annual proportion of RA patients migrating out of the CPRD remained below 5% for all the years under study.

Related to this point is that etanercept and infliximab prescriptions are not administered or captured in the primary care setting and were therefore not available for analysis. Whilst anecdotally the speed and intensity of therapy uptake was subject to regional

Table 2
Estimated difference (per 1000 person years) in joint replacement rates following approval of TNFi in England and Wales

Outcome	Without intervention ^a	With intervention ^a	Absolute difference ^b		
			Estimate	Lower 95% CI	Upper 95% CI
Total hip replacement	5.63	6.57	0.95	−2.66	4.56
Total knee replacement	12.92	8.51	−4.41	−6.88	−1.94

^aPost-NICE TA 36 midpoint estimate (June 2006).
^bCalculated by comparing estimated values for midpoint of post-intervention period to counterfactual values for the same time point (i.e., post-intervention midpoint values estimated based solely on extrapolation of pre-intervention level and/or trend). Estimated from parsimonious models.

variation, it's been previously reported that by 2005 approximately 8500 RA patients on TNFi had been recruited to the British Society for Rheumatology Biologics Register (BSRBR-RA) [51]. For this reason we used a 2-year lag as a sensitivity analysis to allow for delayed implementation, which remained consistent with the overall finding of reduced incidence of TKR but not THR in the biologic era. The use of Joinpoint regression indicated a downward inflection was best-placed at the time point 6–12 months prior to NICE TA 36. This may suggest some role for the 2001 British Society for Rheumatology guidelines (upon which NICE TA 36 were based), although given the close temporal proximity this cannot be determined.

The trend change in THR rates as identified in the Joinpoint analysis was not consistent with the main analysis and was likely the product of particularly low values for the last two time points (Fig. 2A). This finding warrants further investigation regarding these methods, notably the sensitivity to the number of time points in pre- vs. post-intervention periods and the number of outcome events occurring per time point. We are currently exploring these issues with the use of simulated data. Further work will also include estimating the impact of TNFi therapies using healthcare data outside the UK with the inclusion of a non-RA control group.

Another caveat to our results is that they pertain to joint replacements within the first 5 years after RA diagnosis and so it is possible we have underestimated the impact of TNFi therapy by not considering longer-term outcomes. A fixed 5-year time window across the study period was used to prevent THR and TKR rates over time being influenced by underlying variation in the length of follow-up available (i.e., the bias of patients at the beginning of the study period systematically having longer enrollment in the database).

Our study also has several strengths. We studied a large sample of RA patients identified from a data source generalizable to the UK population in terms of age, sex, and ethnicity [23]. Rather than describing temporal trends of RA as an indicator for THR/TKR surgery, we consider our approach of using RA patients as the denominator to be preferable because this accounts for underlying changes in the incidence of RA over time. The interrupted time-series analysis is another strength as this quasi-experimental method controls for secular trends in the outcome prior to the intervention [21,28], and allows for comparison with counterfactual values. The importance of this approach is evident given that a conventional before–after comparison of time-to-TKR using a Cox regression model would have here masked the positive association and yielded no significant difference as there are two almost equal but opposite trends in existence (Fig. 2B). The linkage to HES allowed us to carry out an internal validation of CPRD coding of THR and TKR, which we also supplemented by estimating the 5- and 10-year cumulative incidence of a combined THR/TKR outcome (results not shown) that were very similar to reports from previous UK early RA inception cohorts, at approximately 7% and 12%, respectively.

In conclusion, we have demonstrated that approval of TNFi therapies in England and Wales was temporally associated with a significant and clinically meaningful decline in TKR incidence but no change in THR incidence among early (first 5 years post-diagnosis) RA patients.

Acknowledgments

Study design: D.P.A., S.H., A.J., C.J.E., N.K.A., C.C. Study conduct: S.H., D.P.A., R.C., L.D., A.D., A.J. Statistical analysis: S.H., D.P.A., A.J. Data interpretation: D.P.A., S.H., L.D., R.C., A.S., C.J.E., N.K.A., C.C. Drafting manuscript: S.H., D.P.A. Revising manuscript: all authors. Approving final manuscript: all authors.

The authors would like to thank Miss Susan Thwaite (National Rheumatoid Arthritis Society) for her role as patient and public representative and her role in the study steering committee.

D.P.A. is funded by a National Institute for Health Research Clinician Scientist award (CS-2013-13-012). This article presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

R.C. reports grants from The Danish Rheumatism Association and from The Bjarne Jensen Foundation. L.D. reports personal fees from UCB, from MSD, from UCB, and from MSD. C.E. reports grants and personal fees from Pfizer, from Biogen and from Abbvie, and personal fees from UCB, from Roche, from Janssen, from Samsung bioepis, from Sandoz, from Celltrion, and from Mundipharma. N.K.A. reports grants from BIOIBERICA and personal fees from BIOVENTUS, from REGENERON, and from SMITH & NEPHEW. C.C. has received consultancy fees and honoraria from Amgen, Danone, Eli Lilly, GSK, Medtronic, Merck, Nestle, Novartis, Pfizer, Roche, Servier, Shire, Takeda and UCB. A.J. reports personal fees from Data Safety and Monitoring Board, from Servier, from UK Renal Registry, from IDIAP Jordi GOI, Freshfields Bruckhaus Deringer and grants from Roche. D.P.A. reports grants from Amgen, from UCB Biopharma, and from Les Laboratoires Servier. S.H., A.D. and A.S. have nothing to disclose.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.semarthrit.2017.09.006>.

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